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DOI:

[10.1056/NEJMcibr1607950](https://doi.org/10.1056/NEJMcibr1607950)

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*Citation for published version (APA):*

Persaud, S. J., & Jones, P. M. (2016). A wake-up call for type 2 diabetes? *New England Journal of Medicine*, 375(11), 1090-1092. <https://doi.org/10.1056/NEJMcibr1607950>

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## CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***A Wake-up Call for Type 2 Diabetes?**

Shanta J. Persaud, Ph.D., and Peter M. Jones, Ph.D.

The incidence of diabetes is increasing at an alarming rate, with a predicted worldwide incidence of more than 640 million people by 2040. The vast majority of persons with diabetes have type 2 diabetes, which occurs when insulin resistance is present in fat and muscle cells, hepatic glucose output is enhanced, and insulin secretion fails to compensate. A direct link between obesity and the development of type 2 diabetes is well established, but there is also a strong heritability component. Genetic studies have identified more than 150 so-called risk alleles for type 2 diabetes — variations in genes that increase a person's susceptibility to diabetes.

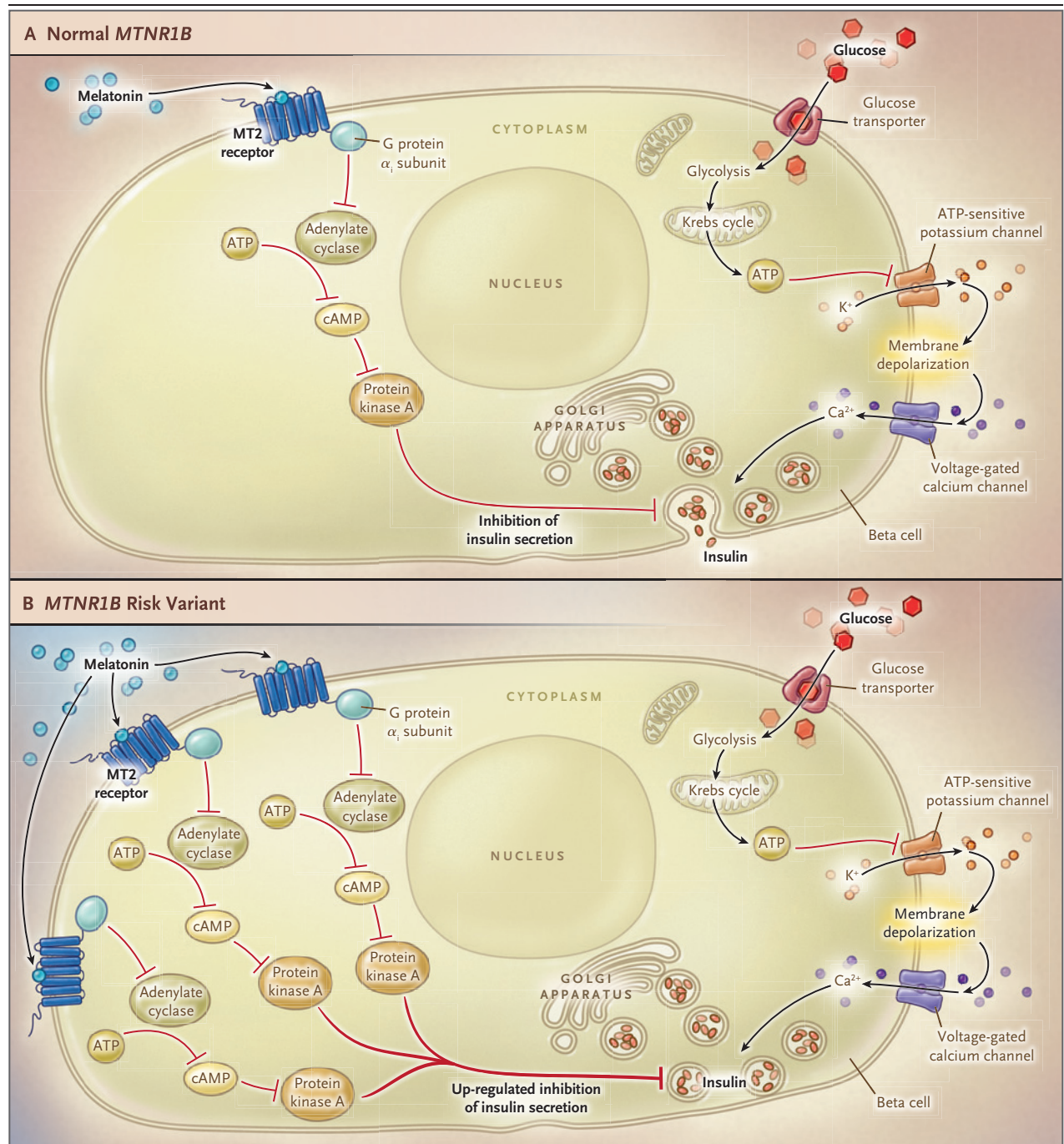
The majority of these gene variants affect genes encoding intracellular proteins that mediate the secretion of insulin by beta cells or that transduce the effects of insulin in target tissues. However, not all candidate genes encode proteins that function within the cell: one that does not is *MTNR1B*, which encodes MT2, a cell-surface G-protein-coupled receptor (GPCR). This receptor is expressed on islet beta cells and is activated by changes in circulating levels of the pineal-derived hormone melatonin. Persons who have a variant of *MTNR1B* are at increased risk for the development of type 2 diabetes,<sup>1</sup> and a recent study by Tuomi and colleagues,<sup>2</sup> who discovered the genetic association, investigated the effects of melatonin, by means of the MT2 receptor, on beta-cell function.

This group screened islets that were isolated from pancreases of organ donors and found that persons who had the *MTNR1B* risk variant also had higher levels of *MTNR1B* messenger RNA in their islets than those without the variant. They also found that the administration of melatonin to rat beta cells that overexpress this receptor inhibited the glucose-induced secretion of insulin. They went on to discover that melatonin reduced

the levels of cyclic AMP in rat beta cells, a finding that is consistent with the known consequences of MT2-receptor coupling (Fig. 1). These observations suggest that up-regulation of the islet MT2 receptor in persons with the *MTNR1B* risk allele is associated with reduced insulin secretion that, in vivo, may result in an impaired capacity to regulate blood-glucose levels properly.

The particularly exciting part of their study is an analysis of the effects of melatonin supplementation on glucose metabolism in persons who are homozygous for the *MTNR1B* risk allele and in persons who are homozygous for the alternative ("nonrisk") allele. Tuomi and colleagues found that a daily dose of melatonin for 3 months significantly reduced first-phase glucose-induced insulin secretion in oral glucose-tolerance tests in all trial participants, as compared with baseline values before treatment with melatonin. There was also a suggestion of an enhanced inhibitory effect of melatonin in persons who were homozygous for the *MTNR1B* risk allele, as compared with the effect of melatonin in persons who were homozygous for the alternative allele, although it is not clear whether the authors applied a test to determine whether this apparent enhancement was significant. The inhibition of insulin secretion is probably mediated by the direct activation of beta-cell MT2 receptors by melatonin, a mechanism that is consistent with the results of the in vitro experiments with rat beta cells.<sup>2</sup> Further experiments with isolated human islets may be required in order to define the direct effects of melatonin on beta-cell function more fully; intriguingly, an earlier report suggested that melatonin stimulates the release of insulin from human islets in vitro.<sup>3</sup>

Melatonin is normally released from the pineal gland at night to entrain circadian rhythms. Its pattern of secretion is disrupted by abnormal



**Figure 1. Effect of Variant *MTNR1B* on Melatonin Signaling in Islet Beta Cells.**

Pancreatic-islet beta cells express MT2 receptors that are encoded by the *MTNR1B* gene. Under normal conditions, melatonin, which is released from the pineal gland at night, binds to this receptor to reduce ATP conversion to cyclic AMP (cAMP) by the enzyme adenylate cyclase. This situation results in reduced activation of the stimulatory protein kinase A, so insulin secretion in response to glucose metabolism is inhibited (Panel A). In persons who have a variant in *MTNR1B* that is associated with risk of type 2 diabetes, MT2 receptors are up-regulated on islet beta cells, which effects a more robust inhibition of cAMP generation and therefore greater inhibition of glucose-stimulated insulin secretion than in those without the variant (Panel B). This reduction in insulin release may be exacerbated by elevations in circulating melatonin, especially in persons who have the *MTNR1B* risk variant, in whom greater numbers of MT2 receptors are expressed than in persons without the variant.

sleep patterns, and epidemiologic studies have shown associations between shift work and susceptibility to type 2 diabetes.<sup>4</sup> Melatonin supplements are often used to treat insomnia or jet lag. Should we be alarmed, therefore, by the finding that melatonin supplementation impairs the glucose-induced secretion of insulin? We should not. The data described by Tuomi et al. indicate that a daily intake of 4 mg of melatonin over a period of 3 months did not substantially impair glucose tolerance, as compared with baseline, and that blood-glucose levels returned to normal within 2 hours after dosing. Melatonin supplementation for jet lag is usually taken for only a few days, and for treatment of insomnia it is taken at doses that are less than 4 mg daily, so any deterioration in insulin release is unlikely to be as marked as that seen in the trial reported by Tuomi and colleagues.

Nonetheless, the study raises the question of whether the gain-of-function variant in *MTNR1B* could predispose persons to glucose intolerance or type 2 diabetes under conditions of insulin resistance such as obesity, in which beta cells are required to compensate for reduced insulin sensitivity by secreting more insulin and may be hindered in doing so by melatonin supplementation. Further studies testing the effects of melatonin on glucose intolerance in obese persons are warranted.

The study also raises the question of whether MT2-receptor antagonists could be developed as therapies for type 2 diabetes, to maximize the

glucose-induced insulin-secretory response by blocking the inhibitory cascade that is activated by melatonin in beta cells. This question is certainly worthy of consideration, but MT2 receptors are expressed in a range of extrapineal tissues, both central and peripheral, which raises the specter of off-target effects. The identification of *MTNR1B* variation as a risk factor and the MT2 receptor as a potential therapeutic target is exciting, but it is worth bearing in mind that this receptor is just one of nearly 300 GPCRs that are expressed by human islets<sup>5</sup> and that other GPCRs may also be good candidates. The fact that agonists of the glucagon-like peptide 1 receptor are routinely used to treat type 2 diabetes supports this point.

Disclosure forms provided by the authors are available at [NEJM.org](http://NEJM.org).

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1. Lyssenko V, Nagorny CL, Erdos MR, et al. Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat Genet* 2009;41:82-8.
2. Tuomi T, Nagorny CL, Singh P, et al. Increased melatonin signaling is a risk factor for type 2 diabetes. *Cell Metab* 2016;23:1067-77.
3. Ramracheya RD, Muller DS, Squires PE, et al. Function and expression of melatonin receptors on human pancreatic islets. *J Pineal Res* 2008;44:273-9.
4. Knutsson A, Kempe A. Shift work and diabetes — a systematic review. *Chronobiol Int* 2014;31:1146-51.
5. Amisten S, Salehi A, Rorsman P, Jones PM, Persaud SJ. An atlas and functional analysis of G-protein coupled receptors in human islets of Langerhans. *Pharmacol Ther* 2013;139:359-91.

DOI: 10.1056/NEJMcibr1607950

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